ABSTRACT

A method of treating a microbial inflammatory encephalopathy condition in a patient is disclosed. The method has the steps of (1) preparing a composition comprising a D peptide and a pharmaceutically acceptable carrier and (2) administering the composition to the patient in a therapeutically effective dose. The D peptide further comprises the general structure: A-B-C-D-E-F-G-H in which:

A is Ala, or absent,
B is Ser, Thr or absent,
C is Ser, Thr or absent,
D is Ser, Thr, Asn, Glu, Arg, Ile, Leu,
E is Ser, Thr, Asp, Asn,
F is Thr, Ser, Asn, Arg, Gln, Lys, Trp,
G is Tyr, and
H is Thr, Ser, Arg, Gly.

All of the amino acids are the D stereoisomeric configuration.
**FIG. 1**

Graph showing Percent of MCP-1 Chemotaxis against CONC M log10.

- (dASTTNYT-NH₂), RAP-101
- All-D-(TTNYT), RAP-103
- All-D-ASTTNYT, RAP-106
- All-D-DAPTA, RAP-107

LogEC₅₀ values:
- RAP101 1.3 e-12M
- RAP103 2.2 e-12M
- RAP106 6.5 e-12M
- RAP107 3.4 e-11M
PEPTIDES FOR PROGRESSIVE TREATING MULTI-FOCAL LEUKOENCEPHALOPATHY AND RELATED CONDITIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 61/816,565, filed Apr. 26, 2013.

[0002] The present invention relates broadly to the treatment of inflammatory encephalopathies. In particular embodiments the invention relates to the prevention or treatment of neurodegenerative or de-myelinating illness associated with viral infection of the brain, an example of which is progressive multi-focal leukoencephalopathy (PML). Other viral infections of the brain may also cause encephalopathies, such as the Arboviruses, which are transmitted by blood-sucking insects such as mosquitoes. In the U.S., mosquito-borne encephalitis infections include West Nile encephalitis, Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis, La Crosse encephalitis. Herpes (HSV-1 and 2) and other herpes viruses that may cause encephalitides include the Epstein-Barr virus, which commonly causes infectious mononucleosis, and the varicella-zoster virus, which commonly causes chickenpox and shingles. Common childhood infections such as measles, mumps, and German measles (rubella), and Entroviruses like coxsackievirus and the, lentiviruses like HTLV-1, or HIV-1 and 2, as some examples. Bacteria, fungi, and parasites may also cause encephalopathies which may be treated by these inventions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] FIG. 1 illustrates that all-D-pentapeptide analogs of Peptide T inhibit CCL2 mediated human monocyte chemotaxis.

[0004] PML, a demyelinating disease of the Central Nervous System (CNS), occurs as a result of widespread brain lesions due to infection of oligodendrocytes by a human polyomavirus (papovavirus virus family) called the JC virus after John Cunningham, from whom it was first isolated. PML is found almost exclusively in individuals who are immunosuppressed: with AIDS, hematological, lymphoreticular malignancies, autoimmune rheumatological diseases, multiple sclerosis (secondary to immunosuppressive treatment) and in those undergoing organ transplantation. The immune therapies with monoclonal antibodies including Natalizumab, rituximab and other immunosuppressants including prednisone, methotrexate, cyclophosphamide and cyclosporine may also be initiating factors in the development of PML.

[0005] Additional reports found that patients taking fingolimod (Gilenya) as well as BG-12, also known as an oral form of dimethyl fumarate (Teefidera), newer treatments for MS, were also associated with PML.

[0006] The clinical presentation of PML may differ: while the MRI may show multifocal pathology, the clinical presentation is typically insidious, with steady progression of focal symptoms that include speech, cognitive, behavioral, motor (head tremor) and visual impairment. PML evolves over several weeks, with a more rapid progression than AIDS dementia complex. It may also involve the brainstem, particularly in PML associated with AIDS than with other entities. Initial lesions may expand, with weakness of a single leg progressing to hemiparesis.

[0007] The viral infection in oligodendrocytes, which help makes myelin in the CNS, is lytic. It undergoes DNA replication and synthesis of viral capsid proteins inside the cell; the virus then infects other cells from a central nidus in a circumferential manner, leading to the expansion of demyelinating lesions. Astrocytes that are infected by JC virus enlarge and develop a distortion of the nuclei with enlargement of multiple nuclei, and may resemble tumor cells in giant cell astrocytomas. However, the main pathology is in the demyelination that occurs. HIV gene products such as Tat can possibly trans-activate the JC viral promoter directly, thus providing an additional pathogenic mechanism beyond general immunosuppression.

[0008] There are no approved treatments for PML and the illness is typically fatal. The principle approach is antiretroviral therapy (ART) if HIV positive, although antiretroviral therapy does not treat PML, or cessation of any immunosuppressive treatments. The basis for ART use in PML is to block HIV and thereby prevent immune suppression, which is the true risk factor as JCV is an opportunistic infection which is normally indolent in non-immunosuppressed, normal populations.

[0009] Treatment of PML by cessation of immunosuppressive therapies, such as in MS patients treated with Natalizumab is associated with an Immune reconstitution inflammatory syndrome (IRIS), also called immune restoration disease. Return of immunocompetence may cause worsening of symptoms and neurological disease in patients with opportunistic infections, which can be severe, even fatal. Even in those who survive, disabilities typically persist and recovery is partial. An unmet medical need is to prevent or treat IRIS reactions.

Pre-Clinical Studies that Show RAP-101 Blocks JCV Replication In Vitro

[0010] Prior laboratory and clinical studies with RAP-101 demonstrate that RAP-101 inhibits the replication by the JC virus as shown in Table 1. Note that RAP-101 is the monomeric form of [D-A₁,S-T-T-T-N₆], where amino acids are indicated by their single letter abbreviations and the alanine in position 1 is a D-amino acid not an L-amino acid.

| TABLE 1 |
| IN VITRO EFFECT OF D-ALA₁-PERIDEPTIDE T-NH₂ ON JCV REPLICATION IN CULTURED CELLS INFECTED WITH JCV. |

<table>
<thead>
<tr>
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<td>20</td>
<td>44</td>
<td>45</td>
<td>40</td>
</tr>
</tbody>
</table>

The data above are expressed as percent of cells positive at each time point.

[0011] Additionally, these experiments suggest that RAP-101 also down-regulates the synthesis of the viral early gene, T antigen as shown in Table 2. Down-regulation of T antigen expression prevents the switch to DNA replication and late viral gene expression and may be an explanation for the anti-viral effects of RAP-101.
TABLE 2

IN VITRO EFFECT OF TO D-ALA1-PEPTIDE T-NH2 ON JCV REPLICATION IN CULTURED CELLS INFECTED WITH JCV ON T-ANUGEN (A VIRAL PROTEIN) EXPRESSION

<table>
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<th>RAP-101 Concentration µg/mL</th>
<th>Days</th>
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<tbody>
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<td>0.0001</td>
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<td>Control</td>
<td>47</td>
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[0012] U87MG cells infected with JC virus were cultured in the presence of RAP-101 at the indicated concentrations. Cytokine synthesis was measured in supernatant at days 3, 7, and 21 using ELISA capture assays. Infected cells synthesized TNFα and TGFβ at least 10-fold over baseline. The results demonstrate that RAP-101 at concentrations of 12 to 0.01 µg/ml resulted in down-regulation of TNFα, TGFβ, and IL-6, but had no effect on IL-4 levels. The data is shown in Table 3.

TABLE 3

INFLAMMATION CONTRIBUTES TO PML PROGRESSION AND THE RESULTS SUGGEST BENEFICIAL MECHANISMS IN TREATING PML AND OTHER INFLAMMATORY BRAIN DISEASES WITH ELEVATED CYTOKINES

<table>
<thead>
<tr>
<th>RAP-101 Concentration µg/mL</th>
<th>TNF-α</th>
<th>TGF-β</th>
<th>IL-6</th>
<th>IL-4</th>
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<tbody>
<tr>
<td>12.0</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
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<td>Control</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Legend: ↓ = down-regulated ↑ = up-regulated → = no change

[0013] U87MG cells infected with JC virus were cultured in the presence of RAP-101 at the concentrations shown in the first column. Cytokine synthesis was measured in supernatant at days 3, 7, and 21 using ELISA capture assays. Infected cells synthesized TNFα and TGFβ at least 10-fold over baseline. The results demonstrate that RAP-101 at concentrations of 12.0 to 0.01 µg/ml resulted in down-regulation of TNFα, TGFβ, and IL-6, but had no effect on IL-4 levels.

[0014] Further studies show RAP-101 alters immediate early gene expression in U87MG cells. Specific examples include that RAP-101 reduces c-Jun expression at 4 hours in uninfected cells. In infected cells RAP-101 blocks up-regulation of c-Jun expression induced by JCV infection of U87MG cells.

[0015] RAP-101 up-regulates egr-1 expression at 4 hours and reduces egr-1 expression at 16 hours in uninfected U87MG cells. In infected cells RAP-101 up-regulates egr-1 expression at 4 hours in JC virus infected U87MG cells and blocks egr-1 up-regulation by JC virus at 16 hours. The temporal alterations of egr-1 expression are likely to alter the expression of other egr family members which are induced later in IEG expression. RAP-101 does not alter c-fos expression in either JC virus-infected or uninfected U87MG cells.

[0016] The inventors believe, but do not want to be held to this, that a mechanism of action of RAP-101 to suppress JCV replication involves suppression of immediate early genes. An additional mechanism may involve antagonism of chemokine receptors such as CCR5 or others because in PML prominent expression of MIP-1alpha and CCR5 are found within areas containing histopathological lesions.

Clinical Benefits in PML Patients

[0017] Life extension: A total of seventeen HIV+ PML patients have been treated with intravenous D-ala1-peptide T-NH2, for a period of 2 weeks through 12 years. At the time of those patients PML occurred largely in immunosuppressed HIV patients who had a typical 3-6 month life expectancy after PML is diagnosed. PML patients treated with D-ala1-peptide T-NH2, also called RAP-101, and before that “DAPTA”, lived longer than expected. Thus 41% (17/41) of patients in survived beyond six months. 17% (10/59) of the Protocol 1 patients survived beyond five years. Three patients received sequential MRI’s. In all three cases the MRI’s demonstrated a lack of progression after three months of treatment. By then end of two years PML could no longer be detected in two patients by brain biopsy or in the cerebral spinal fluid.

[0018] In a further study, Protocol 2, 50% (7/14) additional patients tested survived beyond six months. MRI’s demonstrated a lack of progression at three months in both of these patients. PCR analysis of the CSF at six months in both patients was non-detectable for the JC virus. Both patients continued to survive in good clinical condition through 3 years post study follow-up. PML brain lesions began to reduce in size and number between 6 and 9 months of treatment. Magnetic Resonance Spectroscopy was able to demonstrate chemical changes in the brain starting at 6 months. The patients received D-ala1-peptide T-NH2/RAP-101 at doses from 3 to 24 mgs per day, as continuous infusions, or nasal spray delivery. Effective doses are expected to be 0.01 to 250 mgs per day, depending on route: nasal, IV, sub-cutaneous, oral, buccal, rectal. An intravenous or any parenteral route may be used.

Clinical Benefit of D-ALA1-Peptide T-NH2

[0019] Forty percent (8) of the 20 enrolled subjects survived six months or more beyond initial PML diagnosis. This data is shown in Table 4.

TABLE 4

SURVIVAL OF PML PATIENTS ON D-ALA1-PEPTIDE T-NH2 TREATMENT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment (Days)</th>
<th>Status at End of Study</th>
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<tbody>
<tr>
<td>001</td>
<td>&gt;3,650</td>
<td>ALIVE*</td>
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<tr>
<td>023</td>
<td>&gt;2,590</td>
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<tr>
<td>004</td>
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<td>019</td>
<td>&gt;910</td>
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<td>&gt;275</td>
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<tr>
<td>022</td>
<td>212</td>
<td>ALIVE</td>
</tr>
</tbody>
</table>

*This patient is alive and well over thirteen years since his PML diagnosis.
Table 4 shows that four of the 8 patients showed no progression by MRI and two showed no evidence of PML by MRI or CSF viral load testing by JCV PCR at the end of treatment.

D-Ala1-Peptide T-NH2 (RAP-101) exerts these patient benefits, accordingly, any molecule related to DAPTA, that may share its specific affinity to CCR5, and the highly related (85% homology) CCR2, is a candidate to have important and useful pharmacological applications, not only to treat viral infection, but also to treat the maladies associated with the inflammatory pathway, i.e., such as occurs in PML, TSP, Alzheimer’s disease, psoriasis, multiple sclerosis and other conditions, both chronic and acute.

By analyzing the structure of DAPTA, the inventors deduced that a family of related peptides were candidates for having therapeutic properties. Preferred compositions are pentapeptides derived from the HIV-1 or 2 envelope proteins glycoproteins gp160 and gp120, or other lentiviruses such as HTLV-1. Some examples are indicated in Table 5, which comes from the publication [Ref Ruff, M. R., M. Polianova, C. B. Pert, and F. W. Ruscetti. 2003. Update on D-Ala-Peptide T-Amide (DAPTA): A Viral Entry Inhibitor that Blocks CCR5 Chemokine Receptors. Curr HIV Res. 1:51-67]. And shows the action of the peptides to block viral (HIV) infection via the CCR5 receptor.

Further examples of diverse V2 peptides of this family are shown in Table 6, which provides examples that these peptides are potentially bioactive, having neuroprotective effects against HIV viral envelope proteins [Brenneman, D. E., J. M. Buzy, M. R. Ruff, and C. B. Pert. 1988. Peptide T sequences prevent neuronal cell death produced by the envelope protein (gp120) of the human immunodeficiency virus. Drug Devel Res. 15:361-369].

<table>
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<tr>
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<td>Epstein-Barr</td>
</tr>
<tr>
<td>TTNYT (SEQ ID NO: 15)</td>
<td>inactive</td>
<td>synthetic</td>
</tr>
</tbody>
</table>
The peptides of Tables 5-6 are only precursors for useful drugs as they are expected to be quickly destroyed by proteases in the body in any therapeutic administration.

In order to overcome this limitation we hereby disclose an unexpected method of preserving potency. An initial demonstration of utility is shown in FIG. 1, where antagonism of chemokine receptor system CCR5/CCR2 is blocked by D-alal-peptide T-NH2, aka “DAPTA”, the expected result (Redwine, L., C. B. Pert, J. D. Rone, R. Nixon, M. Vance, B. Sandler, M. D. Lampkin, D. J. Dieter, and M. R. Ruff, 1999. Peptide T blocks GP120/CCR5 chemokine receptor-mediated chemotaxis. *Clin Immunol.,* 93:124-131) and unexpectedly the all-D-amino acid octapeptide analog of ASTTNTYN (SEQ ID NO:1) (Peptide T), the pentapeptide derivative of Peptide T (all-D-ASTNTYN) (SEQ ID NO:2), and the all-D-amino acid version of D-alal-peptide T-NH2. The structures may be organized as below, for ease of viewing, in reference to the parent compound Peptide T (ASTTNTYN) (SEQ ID NO:1) described in Pert, 1985, comprised of the normal L-form of amino acids and which is unstable for clinical use.

```
ASTTNTYN (Peptide T)
(D-A1)STTNTYN-NH2
(all-D)-ASTTNTYN
(all-D)-ASTTNTYN-NH2
(all-D)-TTNTY
```

The all-D substitution results in an approximately 2-5-fold lower potency, which is a minimal loss of activity. Prior work showed that making two D-substitutions in peptide T, to form (D-A1, D-T3)-peptide T-NH2 resulted in over 100,000-fold loss of potency (Pert, 1985). Thus it is was unexpected that converting ALL the amino-acids to D form would retain substantial potency to block chemokine receptors.

Thus the substitution of D-amino acids for all of the L-amino acids in the sequence in order to retain activity and stability to protease degradation are non-obvious. In the example above, one D substitution in a key spot (TTNTY) caused loss of all activity and that substitution, when retained in an all-D-variant, is no longer lethal to potency. Thus a further aspect of the invention is to disclose all-D-amino acid containing peptides related to D-alal-peptide T-NH2, such as those of the list above, as they have comparable in vitro receptor potency to D-alal-peptide T-NH2, and a benefit is that such modification to all-D amino acids protects to protease degradation and makes the compounds orally effective (see Padi, 2012 for oral efficacy of (all-D)-TTNTYN (SEQ ID NO:2), called RAP-105 in the article, to prevent and reverse neuropathic pain and block inflammation in animals. The use of all-D amino acids seems to be generally useful as several examples were here shown.

As shown above, JC virus infected U87MG cells were treated with varied concentrations of RAP-101 and JCV DNA (FIG. 1) or T antigen (FIG. 2) expression were measured. The results demonstrate that RAP-101 inhibits the replication of JC virus at concentrations from 48 to 0.001 ug/ml and maintaining the cultures in the presence of RAP-101 resulted in viral suppression throughout the 28 day testing period.

HIV gp120 V2 region derived pentapeptides inhibit HIV entry. The gp120 V2 region of diverse HIV-1 and 2 isolates encodes small peptides, homologous to the C-terminal five amino acids of peptide T (ASTTNTYN) (SEQ ID NO:1), which share the ability to block HIV entry in a CCR5 selective manner. The peptides are antagonists of CCR5 and the closely related CCR2. Pentapeptide sequences are indicated by their single-letter codes. These synthesized peptides were tested for their ability to block HIV (92HT596; R5/X4 isolate) entry in MAGI cells via either the CCR5 or CXC4 co-receptor pathways, with details as described in [Ref Ruff, M. R., M. Polianova, C. B. Pert, and F. W. Ruscetti, 2003. Update on D-Ala-Peptide T-Amide (DAPTA): A Viral Entry Inhibitor that Blocks CCR5 Chemokine Receptors. *Curr HIV Res.* 1:51-67]. Infection was determined by counting blue focus-forming units (BFU) 48 hrs later. Data are the means and s.e.m. of triplicate cultures and results are expressed as BFU’s, percent of control (treated/vehicle×100).

The examples show that active peptide sequences may be derived from retroviruses like HIV and HTLV-1, but similar peptides from other viruses including Hepatitis C, Epstein-Barr, and the natural peptide vasoactive intestinal peptide had much reduced, or no biopotency. Additional specificity can be shown in that a modification of changing a single amino acid from L to D form, example peptide TTNTY (SEQ ID NO:15), completely loses activity.

FIG. 1 illustrates the activity of all-D amino acid derivatives of Peptide T. This peptide, the V2 derived antagonist of CCR5/CCR2 mediated HIV infection and inflammation. The FIG. 1 assay measured the peptide’s ability to block CCL2 (MCP-1) chemotaxis. Triplicate determinations were made and results are expressed as the mean plus or minus SEM. The experiment shown is a direct comparison among all RAPs. Statistical analysis was by unpaired t-test, with significance set at the p<0.01 (*) level for difference from CCL2 only chemotaxis.

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1. A method of treating an inflammatory encephalopathy condition in a patient comprising the steps of:
preparing a composition comprising a D peptide and a pharmaceutically acceptable carrier, 
said D peptide further comprises the general structure: 
A-B-C-D-E-F-G-H in which:
A is Ala, or absent, 
B is Ser, Thr or absent, 
C is Ser, Thr or absent, 
D is Ser, Thr, Asn, Glu, Arg, Ile, Leu, 
E is Ser, Thr, Asp, Asn, 
F is Thr, Ser, Asn, Arg, Gln, Lys, Trp, 
G is Tyr, and 
H is Thr, Ser, Arg, Gly, 
and wherein all amino acids are the D stereoisomeric configuration, and administering said composition to the patient in a therapeutically effective dose, wherein said composition acts to treat the inflammatory encephalopathy condition in the patient.

2. The method as defined in claim 1 wherein said inflammatory encephalopathy condition is selected from the group consisting of neurodegenerative illness and de-myelinating illness.

3. The method as defined in claim 1 wherein said inflammatory encephalopathy condition further comprises progressive multi-focal leukoencephalopathy (PML).

4. The method as defined in claim 1 wherein said administering said composition to the patient is selected from the group consisting of administering: orally, buccally, parenterally, topically, rectally, vaginally, by intranasal inhalation spray, by intrapulmonary inhalation.

5. The method as defined in claim 1 further comprising, said D peptide is at most twenty (20) D amino acid residues in length and contains five contiguous D amino acid residues that have a sequence selected from the group consisting of:

<table>
<thead>
<tr>
<th>Sequence</th>
<th>SEQ ID NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser-Ser-Thr-Tyr-Arg,</td>
<td>3</td>
</tr>
<tr>
<td>Thr-Thr-Ser-Tyr-Thr,</td>
<td>4</td>
</tr>
<tr>
<td>Asn-Thr-Arg-Tyr-Arg,</td>
<td>5</td>
</tr>
</tbody>
</table>

6. The method as defined in claim 5 further comprising, said D peptide derivative is at most twelve (12) D amino acid residues in length.

7. The method as defined in claim 5 further comprising, said D peptide derivative is at most eight (8) D amino acid residues in length.

8. The method as defined in claim 5 further comprising, said D peptide is five (5) D amino acid residues in length.

9. A method of treating an inflammatory encephalopathy condition in a patient comprising the steps of:
treating loss of brain function in a patient comprising the steps of:
preparing a composition comprising a peptide analog and a pharmaceutically acceptable carrier, 
said peptide analog is [D-Ala]1-Ser-Thr-Thr-Thr-Asn-Tyr-Thr-NH2, SEQ ID NO:1 in which the first amino acid is a D stereoisomer and the remaining amino acids are L stereoisomers and the last amino acid has an amide cap, and 
administering said peptide analog to the patient in a therapeutically effective dose, wherein said composition acts to treat the inflammatory encephalopathy condition in the patient.

10. The method as defined in claim 9 wherein said inflammatory encephalopathy condition is selected from the group consisting of neurodegenerative illness and de-myelinating illness.

11. The method as defined in claim 9 wherein said inflammatory encephalopathy condition further comprises progressive multi-focal leukoencephalopathy (PML).